REMARKS

Applicants respectfully request reconsideration of the rejections set forth in the Office Action mailed on February 19, 2002. Claims 1-37 have been rejected. Claims 12 and 23 have been cancelled herein without prejudice. Claims 1-11, 13-22, and 24-37 are pending.

This amendment is to expedite prosecution and should not be construed as acquiescence in any ground of rejection. Applicants reserve the right to prosecute the originally filed claims in the future. A clean version of the amended claims with instructions for entry pursuant to 37 C.F.R. §1.121(c)(1)(i) is included above. A marked-up version of the amended claims pursuant to 37 C.F.R. §1.121(c)(1)(ii) is attached as Appendix I. The comments in the Office action are now addressed in turn.

Applicant's Attorney appreciates the courtesies extended by Examiner Chakrabarti in a telephone interview on July 29, 2002. At the interview, the rejections of all of the claims were discussed as well as proposed amendments thereto. We found the discussion to be quite helpful and greatly appreciate the Examiner's willingness to allow us this accommodation.

Rejections under 35 U.S.C. §102

Siciliano et al.

The Office action rejects claims 1-6 and 12-14 under 35 U.S.C. §102 (b) as being anticipated by Siciliano *et. al.* (U.S. Patent 5,538,869). Specifically, it is asserted that Siciliano *et. al.* describe a method of "incubating single stranded forms of the population of nucleic acid fragments under annealing conditions, whereby single stranded forms of nucleic acid fragments having repeat sequences preferentially hybridize to each other relative to nucleic acid fragments lacking repeat sequences." *See* paragraph 5 at page 2 of the Office action. The applicants respectfully traverse this rejection.

Siciliano *et. al.* discuss a method whereby primer sets are used to prepare DNA probes specific for a chromosome for use in painting individual chromosomes in

metaphase cell spreads and interphase nuclei by the "inter-Alu-PCR" method. The methods describe two methods for enriching the probes for chromosomally-specific non-repeat containing DNA sequences prior to application to cells. Both methods employ the hybridization of repeat sequence-rich human DNA (low-Cot DNA) to the probe DNA to be enriched for non-repeat DNA.

In contrast, in the present invention no repeat sequence-rich DNA is added to the nucleic acid fragments that are to be enriched for non-repeat containing DNA. Rather, single stranded forms of the population of nucleic acid fragments are incubated under annealing conditions, whereby those having repeat sequences "preferentially hybridize *to each other* relative to nucleic acid fragments lacking repeat sequences".

It is also asserted by the Office that Siciliano *et. al.* describe a method of "inherently hybridizing the separate single stranded forms of the population of nucleic acid fragments to a nucleic acid probe array." *See* paragraph 2 at page 3 of the Office action. The Examiner indicates that this rejection is "based on the fact that metaphase spreads are nucleic acid probe array". Again, the applicants must respectfully disagree.

Siciliano *et. al.* describe a method whereby non-repeat containing probes are annealed to whole chromosomes. In contrast, the present invention describes a method whereby single stranded form of non-repeat containing nucleic acids are hybridized to a "nucleic acid probe array". A nucleic acid probe array is well known to a person of skill in the art to be a group of nucleic acid probes that is distinct from a metaphase spread, which is a grouping of chromosomes. Probe arrays are discussed in section IV.a. of the application, as well as in the literature referenced in the application (Schena, *Microarray Biochip Technology* (Eaton Publishing, MA, USA, 2000)).

As repeatedly indicated by the courts, anticipation requires that all of the elements and limitations of the claim be found within a single prior art reference. There must be no difference between the claimed invention and the disclosure provided by the reference, as viewed by a person of ordinary skill in the field of the invention. (*Scripps Clinic & Research Fdtn. v. Genentech, Inc.*, 927 F.2d 1565, 1576 [Fed. Cir. 1991]). Furthermore, "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. (*In re Royka*, 490 F.2d 981, 180 USPQ 580 [CCPA 1974].

Thus, based on the information provided *supra*, Applicants respectfully submit that Siciliano *et. al.* do not teach every element of the claimed invention and thus, do not anticipate the claimed invention. Nonetheless, to further the prosecution of the present application, and while reserving the right to prosecute the originally filed (and/or similar) claims in the future, Applicants have amended the claims herein to more explicitly recite the use of nucleic acid probe arrays in the instant invention. Applicants respectfully request that the rejection be withdrawn.

Austin et al.

The Office action rejects Claims 15-18 under 35 U.S.C. §102(e) as being anticipated by Austin *et. al.* (U.S. Patent 6,132,965). Specifically, it is asserted that Austin *et. al.* describe a method for "hybridizing either the tester nucleic acids that do hybridize to the driver population, or the tester nucleic acids that do not hybridize to the driver population to a nucleic acid robe array." *See* paragraph 8 at page 4 of the Office action. Applicants respectfully traverse this rejection.

Austin *et. al.* describe a method whereby hyperhomocysteinemia is diagnosed by a molecular genetic means through the identification of genes which are transcriptionally modulated by the level of a metabolite that correlates with hyperhomocysteinemia. It also presents a method for enriching, isolating and identifying nucleotide sequences of low abundance RNA species that are differentially expressed in individuals having elevated levels of serum homocysteine. Austin *et. al.* describe a subtractive hybridization method that hybridizes driver and tester populations of cDNA molecules to remove sequences from the tester population that also are present in the driver population, but *do not teach* the hybridization of the resulting enriched tester population to a nucleic acid probe array.

As the elements of Austin *et. al.* are not the same as those presently claimed, Applicants submit that Austin *et. al.* do not anticipate the pending claims and respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. §103

Siciliano *et. al.* in view of Arnold *et. al.*

The Office action rejects Claims 1-14 under 35 U.S.C. §103(a) as being anticipated by Siciliano *et. al.* (U.S. Patent 5,538,869) in view of Arnold *et. al.* (U.S. Patent 5,714,354). Specifically, it is asserted that while Siciliano *et. al.* describe the method of claims 1-6 and 12-14, Arnold *et. al.* discuss the separation of nucleic acid fragments by successively performing hydroxyapatite chromatography and HPLC. *See* paragraph 2 at page 8 of the Office action. The applicants must respectfully disagree, asserting that neither of the cited references, alone or in combination, teach the presently claimed methods.

As discussed above, Siciliano *et. al.* do not teach the hybridization of single stranded forms of nucleic acid fragments having repeat sequences "to each other", nor do they describe the hybridization of single stranded forms of a population of nucleic acid fragments to a nucleic acid probe array. The Arnold *et. al.* reference describes methods to purify a polysaccharide using HPLC to remove "nucleic acid contaminants". There is no teaching in Arnold *et. al.* of hybridization of single stranded nucleic acids either to each other or to a nucleic acid probe array. Thus, there is no teaching in either cited reference of the invention claimed herein, even if the references are combined.

Further, the Examiner argues that Arnold *et. al.* describe a method of separating nucleic acid fragments by successively performing hydroxyapatite chromatography and HPLC. As cited by the Examiner, "The final purification step utilizing hydroxyapatite yields a highly purified product as indicated by the HPLC chromatogram and corresponding UV absorbance readings". However, the "purified product" to which Arnold *et. al.* refer is a polysaccharide and not a nucleic acid.

Although the invention of Arnold *et. al.* does use hydroxyapatite chromatography and HPLC to separate nucleic acids *from* a polysaccharide preparation, it does not teach the method of the present invention to use hydroxyapatite chromatography and HPLC to separate single stranded nucleic acids from annealed double stranded nucleic acids.

Applicants also submit that the Examiner must take the references as a whole into consideration (the critical inquiry is whether "'there is something in the prior art as a whole *to suggest* the desirability, and thus the obviousness, of making the combination.'" *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556, 225 USPQ 26 (Fed. Cir. 1985) (emphasis in the original), quoting *Lindemann Maschinenfabrik GMBH v.*

American Hoist & Derrick Co., 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984)). Furthermore, "[i]t is impermissible, within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238, 241, 147 USPQ 391, 393 (CCPA 1965), cited in *In re Hedges*, 228 USPQ 685, 687 (Fed. Cir. 1986).

In sum, the Applicants submit that the claims are unobvious over Siciliano *et. al.* and Arnold *et. al.*, taken either alone or in combination. Thus, the Applicants respectfully request that this rejection be withdrawn.

Austin *et al.* in view of Sytkowski *et al.*

The Office action rejects claims 15-22 and 24-37 under 35 U.S.C. §103 (a) over Austin *et. al.* (U.S. Patent 6,132,965) in view of Sytkowski *et. al.* (U.S. Patent 5,804,382). Specifically, it is asserted that while Austin *et. al.* describe the method of claims 15-18, Sytkowski *et. al.* describe a method wherein (a) the driver and tester population of nucleic acids are genomic nucleic acid sequences, (b) the tester population of nucleic acids are from a genome, and the driver population of nucleic acids are from at least one region of the genome, or a variant thereof from the same species as the genome. *See* paragraph 2 at page 9 of the Office action. Applicants respectfully traverse this rejection, asserting that neither of the cited references, alone or in combination, teach the presently claimed methods.

As discussed *supra*, the primary reference Austin *et. al.* does not teach the hybridization of the resulting enriched tester population to a nucleic acid probe array. Further, Sytkowski *et. al.* also does not teach the hybridization of the resulting enriched tester population to a nucleic acid probe array, and so does not remedy the deficiencies of Austin *et. al.* Sytkowksi *et. al.* discuss a method of subtractive hybridization for identification of differentially expressed genes and differences between genomic nucleic acid sequences, but do not teach a method for utilizing nucleic acid probe arrays for this purpose. Thus, the combination of the references does not provide the teachings necessary to successfully obtain the presently claimed invention since all the elements of

the claimed invention are not disclosed by either of the cited references, alone or in combination. Thus, the Applicants respectfully assert that the Examiner has not established a *prima facie* case of obviousness, and request that the rejection be withdrawn.

Austin *et al.* in view of Sytkowski *et al.* further in view of Cole *et al.*

The Office action rejects claims 15-37 under 35 U.S.C. §103 (a) over Austin *et. al.* (U.S. Patent 6,132,965) (October 17, 2000) in view of Sytkowski *et. al.* (U.S. Patent 5,804,382) (September 8, 1998) further in view of Cole *et. al.* (U.S. Patent 6,183,957) (February 6, 2001). *See* paragraph 2 at page 10 of the Office action. Applicants respectfully traverse this rejection, asserting that the cited references, alone or in combination, do not teach the presently claimed methods.

As discussed *supra*, the primary reference Austin *et. al.* does not teach the hybridization of the resulting enriched tester population to a nucleic acid probe array, nor does Sytkowski *et. al.* remedy the deficiencies of Austin *et. al.* Cole *et. al.* describe a method for isolating a polynucleotide of interest that is present in the genome of a first mycobacterium strain and/or is expressed by the first mycobacterium strain, where the polynucleotide of interest is also absent or altered in the genome of a second mycobacterium strain and/or is not expressed in the second mycobacterium by hybridizing the genomic DNA of the first mycobacterium strain with at least one clone from a BAC (bacterial artificial chromosome) genomic library of the second mycobacterium strain.

Likewise, Cole *et. al.* also does not remedy the deficiencies of Austin *et. al.* Rather than using a nucleic acid probe array to analyze the tester nucleic acids that either did or did not hybridize to the driver population, Austin *et. al.* describe a method to characterize the polynucleotides of interest isolated from BAC clones by insert termini sequencing.

Thus, the combination of the references does not provide the teachings necessary to successfully obtain the presently claimed invention since all the elements of the claimed invention are not disclosed by either of the cited references, alone or in

combination. Applicants respectfully assert that the Examiner has not established a *prima facie* case of obviousness and request that the rejection be withdrawn.

Supplemental IDS

Applicants submit herewith a Supplemental Information Disclosure Statement citing Lovett *et al.*

Lovett et. al. describe a method for the identification of cDNAs encoded by large genomic regions. This method entails immobilization of a YAC clone of a genomic region onto a filter, hybridization of a cDNA library onto the genomic region on the filter, the removal of nonspecific cDNAs from the filter by washing, and the elution, amplification, and cloning of the specific cDNAs. This method is significantly different from that submitted by the applicant in the present application. In the present invention, following hybridization of a tester population of nucleic acids to a driver population of nucleic acids, the tester molecules that do not hybridize to the driver population are separated from the tester molecules that do bind to the driver population, similar to the method described by Lovett *et. al.* However, distinct from the descriptions of Lovett *et. al.*, tester molecules are then hybridized to a nucleic acid probe array as a means to analyze either the tester molecules that hybridized to the driver population, or the tester molecules that did not hybridize to the driver population. Accordingly, there is no need for amplification and cloning of the tester nucleic acids, as required for the method according to Lovett *et. al.* Therefore, in method of Lovett *et. al.* is distinct from that of the present application.

Further consideration of the presently-pending claims in view of the reference cited therein is respectfully requested.

Conclusion

For the reasons set forth above, the Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, please telephone the undersigned collect at 650-625-4555.

Respectfully submitted,

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MARKED UP VERSION OF AMENDED CLAIMS

1. (Amended) A method of analyzing a subset of nucleic acids within a nucleic acid population, comprising:

(a) providing a population of nucleic acid fragments at least some of which have sequences that are repeated more than once in a genome;

(b) incubating single stranded forms of the population of nucleic acid fragments under annealing conditions, whereby single stranded forms of nucleic acid fragments having repeat sequences preferentially hybridize to each other relative to nucleic acid fragments lacking repeat sequences;

(c) separating single stranded forms of the population of nucleic acid fragments from annealed double stranded forms, the single stranded forms being enriched for nucleic acid fragments lacking repeat sequence **and the annealed double stranded forms being enriched for nucleic acid fragments containing repeat sequences**;

(d) hybridizing the separated single stranded forms of the population of nucleic acid fragments**, wherein said separated single stranded forms are enriched for nucleic acid fragments lacking repeat sequence,** to a nucleic acid probe array**, which array comprises a set of probes complementary to a known reference sequence, the reference sequence being the same or a variant of the sequence of a nucleic acid from which the population of nucleic acid fragments was obtained; and**

(e) determining hybridization of the probes to the single stranded forms of the population of nucleic acid fragments**, wherein said single stranded forms are enriched for nucleic acid fragments lacking repeat sequence**, thereby analyzing **said subset of nucleic acids within said nucleic acid population** [the fragments].

13. (Amended) The method of claim **[12]** 1, wherein the determining indicates the presence of at least one variation in a fragment hybridized to the array relative to the reference sequence.

14. (Amended) The method of claim [12] 1, wherein the population of nucleic acids are from a chromosome from a first individual, and the reference sequence[s] is that of a corresponding chromosome from a second individual.

15. (Amended) A method of analyzing a subset of nucleic acids within a nucleic acid population, comprising:

(a) providing driver and tester populations of nucleic acids;

(b) hybridizing the driver and tester populations with each other;

(c) separating nucleic acids from the tester population that hybridize to the driver population from tester nucleic acids that do not hybridize;

(d) hybridizing either the tester nucleic acids that do hybridize to the driver population, or the tester nucleic acids that do not hybridize to the driver population to a nucleic acid probe array, **wherein said array comprises a set of probes complementary to a known reference sequence, the reference sequence being the same or a variant of the sequence of a nucleic acid from which the nucleic acid population was obtained; and**

(e) determining hybridization of the probes to the tester nucleic acids thereby analyzing the tester nucleic acids.

16. (Amended) The method of claim 15, wherein **[driver population of]** nucleic acids **in the driver population** each bear a tag by which **[driver population of]** nucleic acids **in the driver population** can be immobilized to a binding moiety with affinity for the tag.

18. (Amended) The method of claim [17] 16, wherein the separating step is performed by immobilizing the driver population of nucleic acids and tester population of nucleic acids hybridized to the driver population via the tags of the driver population.

35. (Amended) The method of claim 15, wherein the population of driver nucleic acids are mRNA or nucleic acids derived therefrom from a first source, and the population of tester nucleic acids are mRNA or nucleic acids derived therefrom from a

second source[s], the tester nucleic acids that do not hybridize with the driver nucleic acids are hybridized to the array, these tester nucleic acids [s] being enriched for sequence present in the second source and absent in the first source.